REMARKS

The Office Action of March 21, 2006, has been carefully reviewed along with the applied prior art. The claims in the application are now claims 4, 8, 9, 11 and 14-26, including new claim 26 which reads on the elected subject matter. Applicants' claims define patentable subject matter thereby warranting their allowance. Favorable reconsideration and allowance are respectfully urged.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

Claims 14-25 submitted with the last Reply on June 30, 2005, have been held to be directed to an invention patentably independent or distinct from the invention originally claimed, and therefore have been withdrawn from further consideration. The action of the PTO in this regard is respectfully traversed.

New claim 26 has been added which is a linking claim as it depends from and incorporates the subject matter of claim 14. It should moreover be noted that claim 11, elected by original presentation, also depends from claim 14 and constitutes another linking claim.

Applicants accept that claim 25, directed to a method of preparation, is properly restricted from claims 4, 8, 9 and 11.

Applicants otherwise respectfully traverse the restriction and request an examination on the merits of claims 14-23, as well as claims 4, 8, 9, 11 and 26 which have been elected by original presentation.

The present invention relates to and teaches how to modify the surface of individual islets so they can be brought into direct contact with blood without encapsulating the islets, without having to introduce artificial materials such as used by both Wagner and Soon-Shiong, and without causing the blood to clot. In contrast, both Wagner and Soon-Shiong mention heparin as an example of a substance to be used to reduce the deleterious effect of the artificial material used to encapsulate the islets. Both Wagner and Soon-Shiong aim to shield the islets from direct contact with the blood. There is a clear and distinct difference between the present invention and both Wagner and Soon-Shiong.

Claims 1-4, 10 and 11 have been rejected under §102 as anticipated by Wagner. The rejection is respectfully traversed.

Claims 1-3 and 10 were previously deleted and not in the application at the time of the above rejection. Accordingly, applicants need not address the rejection insofar as it applies to deleted claims.

Applicants note that claims 8 and 9 have not been included in this rejection, and applicants accordingly understand that claims 8 and 9 are deemed by the PTO to define novel subject

matter over Wagner. Applicants are proceeding in reliance thereof.

As regards claims 4 and 11, applicants respectfully continue to rely on (1) the Remarks of the Reply of June 30, 2005, respectfully repeated by reference, (2) the Remarks of applicants' communication of March 2, 2004, respectfully repeated by reference, and (3) the declaration under Rule 132 executed in February of 2004 and filed with the communication of March 2, 2004. Applicants elaborate below, and provide further Remarks.

New claim 26 has been added. It is patentable for the same reasons as the other claims as pointed out below.

Wagner discloses and seemingly denigrates a prior micro-capsulation system where the islets are enclosed in the smallest possible capsules (diameter of 0.5 mm) made of alginate complexed with polylysine, noting the English translation of the Wagner description on page 6, lines 7-10. The islets are much smaller (50-300μm), see pg. 7, line 8), so many fit within the moicro-capsules. Wagner teaches providing an "artificial surface" forming a "mono-layer film" over "proteins" which have "selectively accumulate[d], noting page 13 at the bottom.

Further, the product is characterized by the fact that insulin, proinsulin, preproinsulin and/or organic cells (islets of Langerhans, APVD) systems of xenogenic or autogenic origin can

be used as organic immobilized materials (claim 3) placed or introduced in the nerve tract (claim 2).

Wagner teaches the use of encapsulation, e.g. in the trial commencing at the bottom of page 27, 3000 islet cells were encapsulated on two microprotein silicon catheters. This implies that a definite number of cells (typically several hundred) are confined in a capsule, namely a compartment, defined by a semi-permeable membrane. An objective and apparent result of Wagner is platelet aggregation of blood (pg 17-19 of Wagner). This is distinctly different from the presently claimed invention which involves and teaches surface modification of each individual islet without changing the physical configuration of the islet.

The preferred route for transplantation of islets of Langerhans is to inject the isolated islets into the portal vein allowing the islets to settle in the liver. The result from an animal experiment where porcine islets were intraportally transplanted into pigs is found in applicants' specification at page 5, lines 13-20. The method of intraportal transplantation can also be used in humans, and thus it is impossible to use the intraportal route if the cells have been enclosed in capsules of high molecular weight material that are considerably larger in size than the individual cells/islets.

On page 6 of the Official Action, the rejection states that "the applicant has yet to respond to the fact that the instant application points to encapsulation on page 4 to 5 ...".

This is totally irrelevant and misleading. The tubings that are therereferred to are only used as a tool for testing modified islets and has no function whatsoever to encapsulate any islets. Thus, applicants' specification states as follows beginning with the last paragraph on page 4:

> All the in vitro experiments for studies of islets contacting whole blood **were performed in a tubing loop model.** [emphasis added]

This clearly concerns only the apparatus or device in which the experiments were conducted.

> A soluble conjugate prepared by covalent binding... of heparin... is irreversibly bonded on to the amine surface of the tubings. ... . By using such heparin modified tubings it is possible to incubate the tubings with non-anticoagulated fresh human blood... . Unmodified tubings will invariably induce complete clotting at these experimental conditions.

The tubings are so prepared in order that they can be used without causing the blood to clot. This provides an appropriate device for carrying out the experiments disclosed in applicants' specification.

As noted above, the example in Wagner (page 26-29, English translation) describes a silicon catheter with semi-permeable membrane. Wagner describes the well-known problems of using artificial materials in contact with blood, but there is no description of the fact that the islets are thrombogenic and need to be surface modified to avoid instant blood mediated

inflammatory reactions. Wagner relies entirely on different methods to shield off the islets by an artificial material either by hollow fibre systems, catheters or encapsulation (which explains the phrase "may be encapsulated").

The rejection further states (page 6 in official action): "The modified heparin would encapsulate the islets in Wagner." This is totally wrong. The modified heparin will be attached to each individual islet without changing the dimensions, i.e. size, which again is completely different from the technique disclosed by Wagner. This argument has been thoroughly elaborated upon in the declaration of record. This inherent and implicit feature of the present invention, as confirmed in the aforementioned declaration, has now been made explicit in applicants' claims.

Wagner does not anticipate any of applicants' claims. The rejection should be withdrawn and such is respectfully requested.

Claims 1-4, 10 and 11 have also been rejected under §102 as being anticipated by Soon-Shiong. This rejection is again respectfully traversed.

As with the rejection discussed above based on Wagner, applicants need not address the present rejection insofar as previously deleted claims 1-3 and 10 are concerned, leaving only the rejection insofar as it is considered by the PTO to apply to claims 4 and 11. As claims 8 and 9 have not been so rejected,

applicants understand that applicants' claims 8 and 9 are deemed by the PTO to define novel subject matter over Soon-Shiong, and applicants are proceeding in reliance thereof.

As with the rejection based on Wagner discussed above, applicants respectfully repeat by reference earlier remarks of applicants appearing in the present file, and applicants continue to also rely on the aforementioned declaration of Drs. Korsgren, Nilsson and Larsson.

Applicants further remarks as follows: Soon-Shiong teaches the use of encapsulation and the same arguments as put forward above regarding Wagner apply to Soon-Shiong. This document describes a method for chemically modifying polysaccharides such as alginate, and covalently polymerizing the compounds by use of light (see column 3). The cross-linked material can be used in encapsulation processes. Although claim 5 mentions heparin as a possible alternative compound for use in microcapsules, there is no teaching how heparin could be applied to individual islets, only for the use in a modified biocompatible material. Reading Soon-Shiong, like reading Wagner, does not enable one skilled in the art to reach applicants' claimed subject matter.

The presently claimed invention comprises surface modified insulin producing islets. These islets are coated, prior to transplantation, by pre-incubation of islets in a solution of heparin or a fraction or derivative thereof, see

previously amended claim 4 and applicants' specification, page 6, lines 3-6. The coating procedure is an irreversible modification of the islets where heparin molecules, or other clotting preventing agents, are adsorbed to the cell surface in the form of a permeable coating incapable of preventing immunological cross-reactions.

In the applicants' specification, page 1, lines 13-15, and page 2, lines 11-14, it is described that immunosuppressive drugs are used in relation to transplantation, irrespective if the transplantation concerns whole pancreas or islets.

On page 6 of the Official action, it is argued that "it is unclear how the heparin-alginate conjugate of the Corline system differs from the heparin/alginate system of Soon-Shiong." It is perfectly clear that there are distinct differences. Corline's heparin-amine conjugate (not alginate) can be added directly to the culture medium without affecting the dimensions of the islets. In the description of the present invention, page 10, lines 14-20, it is concluded that the surface modification of the islets by heparin is expected to decrease or even eliminate the need for insulin injections. This clearly implies that the surface modification does not change the insulin excretion of the islets. But according to Example 25 in Soon-Shiong, a rather elaborate procedure has to be applied involving co-extrusion and photo-crosslinking. There is no provision that the islets will

remain as individual islets maintaining their original dimensions.

Soon-Shiong does not anticipate any of applicants' claims. Withdrawal of the rejection is in order and is respectfully requested.

Claims 4, 8, 9 and 11 have been rejected as anticipated by newly cited Bennet et al (Bennet). This rejection is respectfully traversed.

Applicants do not understand how this document can be considered an anticipation of any of applicants' claims. Bennet simply discusses the use of systemic heparin (See abstract), i.e. heparin injected into the blood circulation. There is simply no disclosure whatsoever, no hint, no inference of any method of modifying the surface of individual islets.

Thus, Bennet seems to be more in line with the previously applied reference in the name of Lenschow et al. Applicants respectfully note that the rejection based on Lenschow was correctly withdrawn. Similarly, the rejection based on Bennet should be withdrawn, as it has nothing to do with the present invention.

Applicants' claims define novel subject matter over Bennet. Withdrawal of the rejection is in order and is respectfully requested.

Applicants believe that all issues raised in the Office Action have been addressed above in a manner favorable to allowance of the present application. Accordingly, applicants respectfully request favorable reconsideration and early formal allowance.

Respectfully submitted,

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